IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: Frank Grosveld **Confirmation No. 9062**

Serial No.: **Art Unit No.: 1632**

Filing Date: October 24, 2003 **Examiner: Anoop K. Singh**

For: IMMUNOGLOBULIN 1 considered /aks/ 4/21/08

Customer No.: 34132

DECLARATION OF DR. FRANK GROSVELD

1. I am the inventor of the above-identified patent application. I have read the Final Rejection dated as mailed July 9, 2007, and would reply to several the issues raised as follows below.

2. The invention describes methods for the in vivo derivation of heavy chain only antibodies in transgenic non-human mammals in response to antigen challenge. The invention requires a modification to the normal mammalian heavy chain locus such that the CH1 domain is not expressed in the heavy chain following the gene activation as a result of antigen challenge in specialised B-cells. In the absence of a CH1 domain the modified heavy chain cannot combine with light chain even if light chain is present (i.e. in a wild type mouse background) and as a result heavy chain only antibody (devoid of CH1) is secreted and circulates in plasma. B-cell specific expression is necessary for a productive response to antigen stimulation leading to VDJ re-arrangement and, ultimately, secretion of antigen specific heavy chain only antibody (devoid of CH1). This would not occur in other cell types (e.g. skin, muscle, heart)

3. To ensure B-cell specific expression of the transgene, human regulatory elements known to induce B-cell specific expression in non-human mammals are present in the natural human IgH sequence described in the application as filed and used by Janssens et al. At the time of the invention, it had already been established for sometime that the insertion of a human heavy chain locus (comprising the CH1